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Original Article

Simulation of ventricular rate control during atrial fibrillation using ionic channel blockers

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ABSTRACT

Background: The atrioventricular (AV) node is the only compartment that conducts an electrical impulse between the atria and the ventricles. The main role of the AV node is to facilitate efficient pumping by conducting excitation slowly between the two chambers as well as reduce the ventricular rate during atrial fibrillation (AF).
Methods: Using computer simulations, we investigated excitation conduction from the right atrium to the bundle of His during high-rate atrial excitation with or without partial blocking of the calcium or potassium ionic current.
Results: Our simulations revealed differences in rate reduction and repolarization effects between calcium and potassium current blocking and high degree of potassium current blocking required to reduce the ventricular rate during AF.
Conclusions: Our simulation results explain why potassium current blockers are not recommended for controlling ventricular rate during AF.

1. Introduction

Electrical excitation in the heart is initiated in the sinoatrial node and is conducted sequentially to the atria, atrioventricular (AV) node, bundle of His, left and right bundle branches, Purkinje fiber network, and ventricles [1] (Fig. 1A). In the AV node, the electrical conduction speed is approximately 5 cm/s, which is 10 times slower than in the atrium [2]. The slow conduction in the AV node facilitates efficient pumping of blood by creating a delay between atrial and ventricular systole.

Atrial fibrillation (AF) is the most common sustained clinical arrhythmia. One strategy of treating AF is rate control to reduce ventricular rate, which allows AF to persist. Many reports, such as, those from the AFFIRM study [3], suggest that rate control appears to be at least equivalent to another strategy, i.e., rhythm control, within the spectrum of currently available pharmacological therapeutic options. In the rate control therapy, the AV node is the target that determines the ventricular rate during AF. Calcium channel blockers are usually administered to control the ventricular rate, whereas potassium channel blockers are avoided. Calcium channel blockers are expected to reduce AV node excitability due to low expression of *SCN5A*, the gene encoding the sodium current protein Nav1.5 in the compact AV node [4]. On the other hand, potassium channel blockers are expected to prolong the duration of action potential and refractory periods. Class III antiarrhythmic drugs such as ibutilide increase action potential duration (APD) largely by blocking rapidly activating delayed rectifier potassium current [5] without affecting the PR interval in electrocardiogram (ECG). Therefore, longer refractory

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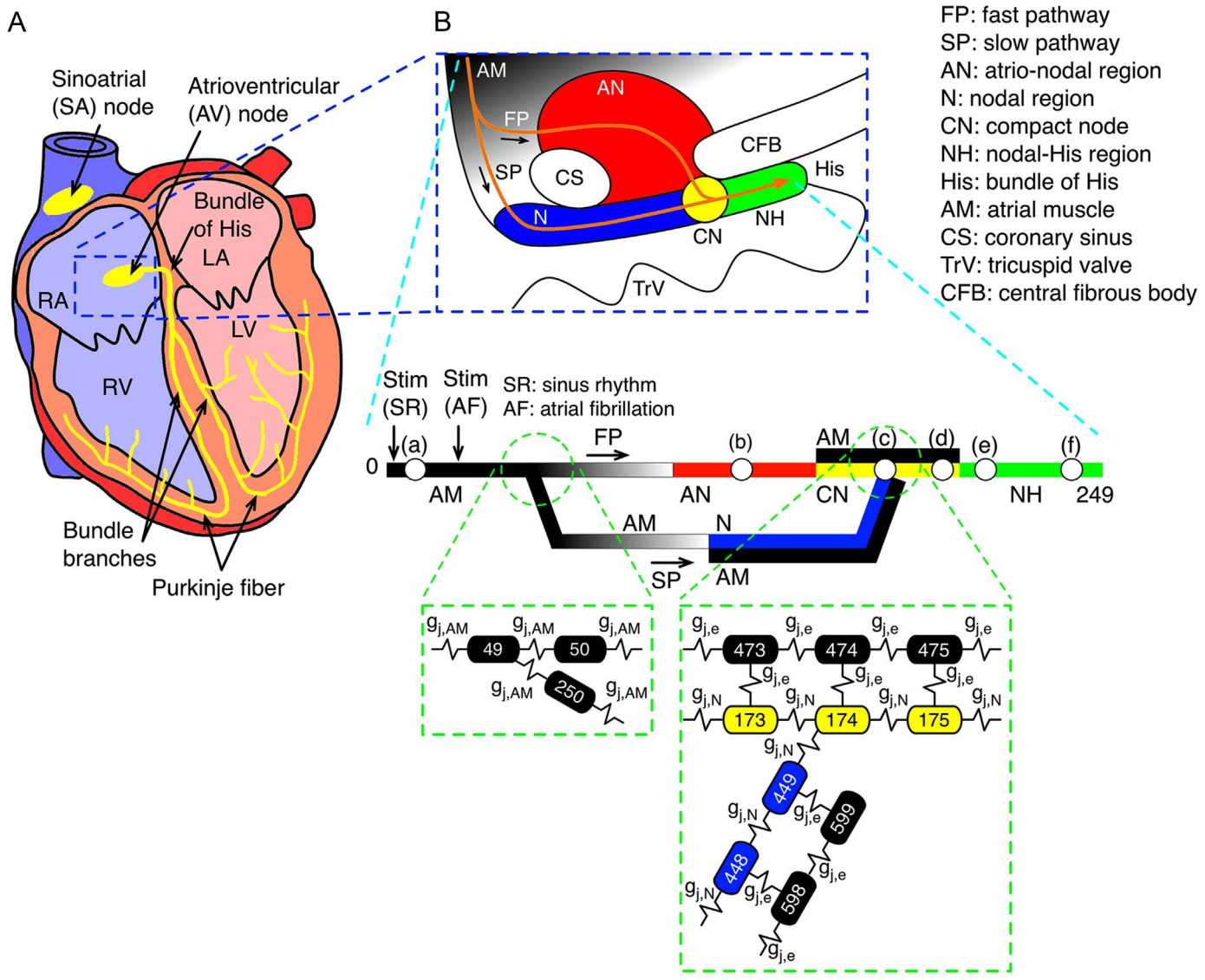

Fig. 1. Relationship between the cardiac conduction system and two types of 1D models. A: The cardiac conduction system. RA: right atrium, LA: left atrium, RV: right ventricle, LV: left ventricle. B: Relationship between the atrioventricular (AV) node (a detailed view is shown) and its one-dimensional model. For details of the models, such as the numbers of units, gap junction conductance, and characteristics of each unit, see the Methods section.

periods are expected to result in less conduction in the AV node when excitation rates in the atrium are high, such as during AF. However, the ionic basis of the rate control is not clearly understood. Understanding how these drugs control the ventricular response during AF may advance clinical treatment strategies. However, it is difficult to observe directly the effects of drugs on electrical excitation conduction in the AV node because non-invasive measurement of the AV node signal is impossible. Computer simulation is one of the methods to solve this problem. Although many electrophysiologically detailed mathematical models are available to simulate action potentials of cardiomyocytes, there are few such models for myocytes in the AV node. Recently, we constructed action potential models for the rabbit AV node, including atrio-nodal (AN), nodal (N), and nodal-His (NH) cells [6]. Using these models and an action potential model of the rabbit atrial myocyte [7], we have constructed a one-dimensional (1D) multicellular model of the region from the right atrium to the bundle of His through the AV node (Fig. 1B). Recently, Boyle et al. conducted a simulation study using Purkinje fibers, whole ventricles, and our AV node 1D model [8].

We also conducted simulations to investigate the mechanisms of excitation conduction in the AV node and ventricular rate control during AF [9]. However, we have not previously analyzed in detail the mechanisms that may explain why calcium channel blockers are suitable for ventricular rate control during AF but potassium channel blockers are not. The study aimed (1) to analyze, in detail, excitation conduction along the AV node to explain the mechanisms of ventricular rate control during AF and (2) to clarify the reason why potassium channel blockers are not efficient in controlling ventricular rate during AF.

2. Material and methods

2.1. Action potential models for rabbit cardiomyocytes

Our 1D AV conduction simulation included four types of action potential models: the atrial cell (AM cell) model developed by Lindblad et al. [7] and the three AV node cell models (the

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